Remarks

Claims 1, 13, 38, 42, 48, 49 and 50 are pending. Claims 3-12, 14-37, 41, 43 and 45-47 have been cancelled by this paper. Claims 2, 39, 40 and 44 were previously cancelled.

In reviewing the specification of the present application, it was noticed the Abstract was not related to subject matter of the specification and claims. To correct this error, a new Abstract has been prepared and the specification amended to bring the Abstract into ambit with the specification and claims. Applicants contend no new matter is added by the new Abstract.

Applicants affirm the provisional election of Group I (cyclopentane fused benzopyrans) where G is C and pharmaceutical compositions, made during a telephone conversation between Examiner John Mabry and Applicants' attorney on August 6, 2007. In view of the new U.S.P.T.O. Rules, 37 C.F.R. 1.75(b), Examination of Claims, Applicants withdraw their provisional traverse and acquiesce to the restriction requirement.

Applicants have amended or deleted claims to restrict the scope of pending claims to provisionally elected subject matter. In addition, clarifying amendments have been made. In Claim 1, the group "$CH(OH)C_1$-C_6alkyl" has been deleted and the group "$C(OH)C_1$-C_6alkyl" substituted for the deleted group. As pointed out by the Examiner, the deleted group was a pentavalent carbon. Fundamentally, Applicants assert one skilled in the art would appreciate there was an error, what the error was, and what the correct group should be. Example 13, page 59, lines 1-20, provides a representative group within the corrected group definition. Applicants have also deleted the term "difluoromethylene" and substituted therefore the group $C=CF_2$. Applicants believe the amendments provide clarity for Example 27, page 94, in view of Example 10, page 53, line 20 through page 54, line 18. Further, Example 26, on page 92, containing a $C=CH_2$ moiety was out of ambit for the definitions of G and has been included by this paper. Applicants respectfully contend these amendments are consistent with the restriction requirement and provisionally elected subject matter and do not add new matter.

Claims 48, 49 and 50 are new and added in this paper. Claim 48 is directed to specific compounds within the ambit of the provisionally elected subject matter. Support for this claim is found at least in Claims (now cancelled) 4, 5, 6, 11, 12 and 14-30. Applicants respectfully contend no new matter is added by this new claim. Claim 49 is directed to a pharmaceutical composition comprising the compound of Claim 13 and a pharmaceutically acceptable carrier. Support for this claim is found at least in Claim 38 and previous Claim 45. Applicants respectfully contend no new matter is added by this new claim.

Claim 49 is new and added in this paper. This claim is generally directed toward a method of using the compound of Claim 13 for treating benign prostatic hyperplasia. This claim is supported at least by Claim 42. Applicants respectfully contend no new matter is added by this new claim.

Objections

The disclosure has been objected to based upon Claim 1, Formula I, the bond from the phenyl ring to the oxygen of the hydroxyl group appearing to be an arrow rather than a single bond.

Although the "arrow" appearance is the result of an ink smudge, for clarity purposes the Formula I presentation in Claim 1 has been amended.

Rejections Under 35 U.S.C. 112, Second Paragraph

A. The inadvertent typographical error in Claim 1, the group "$CH(OH)C_1$-C_6alkyl" has been corrected by amendment and support for the amendment described above. Applicants contend this aspect of the rejection has been properly rectified through this paper.

B. The Examiner's inquiry into the bonding representation in Claim 17 has been rendered moot by the cancellation of that claim. Applicants respectfully contend the Examiner's interpretation of an ethyl group bonded to the cyclopentane ring through an undefined configuration is correct. The bonding representation is defined on page 8, lines 34-35 of the specification.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 42 and 43 were rejected as failing to comply with the enablement requirement. The Examiner provided an analysis under In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) in support of a position of undue experimentation. Applicants traverse the rejection and request reconsideration. Applicants contend, as provided in further detail below, that the specification under a "Wands" analysis provides one skilled in the art with sufficient information to make and use the full scope of the presently claimed invention without "undue experimentation."

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and

use the claimed invention. Even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

The Examiner provided an analysis of those factors pursuant to In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants will address these factors in further detail below:

(1) Breadth of claims:

(a) Scope of the compounds. The Examiner's position is: Owing to the range of primary variables, thousands of cyclopentane-fused benzofurans compounds are embraced.

Applicants' position:

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants respectfully direct the Examiner's attention to page 13, line 9 through page 30, last line, where Schemes A, C (in part), D (in part), F, G, H, I, P, Q, R, S and T are provided. These Schemes and the associated descriptions clearly disclose to one skilled in the art how to make the full scope of compounds contemplated by Claim 1, as amended in this paper. In addition, examples 1, 2, 3, 8-18 and 24-32 are provided describing preparation of specific compounds within the scope of Claim 1. Applicants respectfully contend, they have properly enabled one skilled in the art how to make the full scope of compounds embraced by Claim 1.

(1) Breadth of claims:

(b) Scope of the diseases covered. The Examiner's position is: A method of treating benign prostatic hyperplasia (BPH).

Applicants' position:

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); In re Hitchings, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.

In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

The Examiner's attention is respectfully directed to page 107, line 11 through page 108, line 29, where a description is provided that Applicants contend is more than sufficient to meet the how to use requirement for the full scope of compounds of Claim 1 in treating a "patient" afflicted with benign prostatic hyperplasia.

(2) The nature of the invention and predictability in the art. The Examiner's position is: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor.

Applicants' position:

The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The

relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed.

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which is pertains, or with which it is most nearly connected." The specification need not disclose what is well-known to those skilled in the art and preferable omits that which is well-known to the skilled artisan and already available to the public. In general, post-filing date references should not be used to demonstrate that the patent is non-enabling.

Applicants generally agree the invention is directed toward medicine. The relative skill of those in the art to which the claimed subject matter pertains is high.

(3) Direction or Guidance. The Examiner's position is: That provided is vary limited. The dosage range information is expected to vary from about 0.001 milligrams per kilogram of body weight per day (mg/kg/day) on page 108, lines 15-18 of the specification. Moreover, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for the disease mentioned in Scope.

Applicants' position:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are merely factors in this consideration and are not the controlling factors.

Time and difficulty of experiments are not determinative if they are merely routine.

Applicants respectfully bring the Examiner's attention to the specification at page 107, line 11 through page 108, line 29 and in particular, page 108, lines 1-18. The specification states:

> "A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the

> therapeutically effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. (underlining added)
>
> A therapeutically effective amount of a compound of formula (I) is expected to vary from about 0.001 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts can be determined by one skilled in the art." (underlining added)

Applicants respectfully contend dose/response evaluations in individual mammalian species are routine for those skilled in the relevant art to which the present invention is directed. Applicants also direct the Examiner's attention to their position above regarding (1)(b).

(4) State of the Prior Art. The Examiner's position is: These compounds are substituted cyclopentane-fused benzopyrans. So far as the Examiner is aware, no substituted cyclopentane-fused benzopyrans of any kind have been used for the treatment of the disease mentioned in the Scope.

Applicants' position:

Applicants respectfully contend that to their knowledge, the compounds presently claimed are novel. No "substituted cyclopentane fused benzopyrans" are or have been commercially available to treat benign prostatic hyperplasia (BPH). As pointed out in the specification at page 2, lines 26-28, there are current available medicinal agents used to treat BPH. These agents include alpha andrenergic antagonists for symptomatic relief and steroid 5-alpha reductase inhibitors to reduce hyperplastic tissue bulk.

(5) Working Examples. The Examiner's position is: Applicant shows an ER Binding Assay study with the working examples but no working examples were shown for treating benign

prostatic hyperplasia (BPH).

Applicants' position:

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting an application purporting to disclose how to do it.

The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. A rigorous or an invariable exact correlation is not required.

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner.

As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. As the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use.

Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound, *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980).

If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

If an applicant provides data, whether from *in vitro* assays or animal tests or both, to

support an asserted utility, and an explanation of why that data supports the asserted utility, the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility.

If one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility.

Applicants contend a reasonable correlation between the ER Binding Assay study described on page 103, line 17, through page 104, line 19, of the specification and *in vivo* small animal model benign prostatic hyperplasia treatment has been established. In the Image File Wrapper (IFW) of U.S. Patent 7,217,734, U.S. Application Serial No. 10/493,092, there are three Rule 130, 131 or 132 Affidavit entries dated October 27, 2006. Two of those Declarations, one by Venkatesh Krishnan and one by Blake Neubauer, clearly establish a correlation between the ER Binding Assay and *in vivo* small animal BPH treatment for structurally similar compounds. The present specification at page 104, lines 10-18 describes that the compounds of Examples 1-19 and 22-25 are active in the ER Binding Assay and further discusses binding affinities and selectivity. Applicants respectfully contend the data in the specification are more than sufficient and a reasonable correlation has been established.

(6) Skill of those in the art. The Examiner's position is: The current treatments or maybe no treatment for the treating benign prostatic hyperplasia (BPH) is surgery, while chemotherapeutics provide only symptomatic relief. In 1996, the discovery of estrogen receptor beta (ERβ) initiated intense interest in the scientific community; never-the-less, research into the function of this receptor remains unclear (see page 424, abstract – Endocrinology, October 2003, 144(1):4241-4249).

Applicants' position:

As provided in the specification at page 2, lines 26-29, currently approved drugs for the treatment of BPH include alpha adrenergic receptor blockers. These drugs relax smooth muscles involved in urination and are effective by 12 weeks and can offer symptom improvement as early as one week. Examples of alpha adrenergic receptor blockers are: Cardura (doxazosin) Pfizer/generic at this time; Flomax (tamsulosin) Boehringer Ingelheim; Hytrin (Terazosin) Abbott/generic at this time; and Uroxatral (alfuzosin) Sanofi-Aventis.

A second group of currently approved drugs for the treatment of BPH are 5-alpha

reductase inhibitors. These drugs decrease the size of the prostate and thereby reduce urinary obstruction. These drugs typically take 12-24 weeks to provide symptom improvement. Examples of 5-alpha reductase inhibitors are Proscar (finasteride) Merck; and Avodart (dutasteride) Glaxo Smith Kline.

The current standard for most effective treatment is a surgical procedure termed transurethral resection of the prostate (TURP).

The present invention as embodied in Claim 42 is directed to cyclopentane fused benzopyran compounds (as more particularly defined) for treating benign prostatic hyperplasia (see specification at least at page 1, line 10 through page 2, line 14).

Estrogen receptor beta selective agonist compounds are therapeutically useful for treating benign prostatic hyperplasia. This disease is mediated by the insufficient expression of estrogen receptor beta. Insufficient expression of ER beta allows ER alpha stimulated transcription and cellular proliferation to induce the hyperplastic disease condition.

Applicants contend estrogen receptor beta (ER-beta) was known to exist in the prostate (see specification, page 1, line 20).

ERβ was originally identified, isolated and cloned from a rat prostate cDNA library and prominent expression was found in prostate tissue in males. *Kuiper, et al.*, PNAS, 93, 5925-5930 (1996). The homologous mouse cDNA was also separately cloned using a mouse prostate library, *Tremblay, et al.*, Molecular Endocrinology, 11, 353-365 (1997).

Weihua, et al., Molecular and Cellular Endocrinology, 193, 1-5 (2002) evidences that ER-beta expression in the prostate exerts an antiproliferative function and ER-beta selective ligands (agonists) would be useful in the prevention or clinical management of benign prostatic hyperplasia and/or prostate cancer.

> "In ERβ knockout (βERKO) mice there are foci of epithelial cellular hyperplasia in the ventral prostates at 5 months of age. At around 1 year of age these mice develop neoplasia with morphological resemblance to PIN (prostatic intraepithelial neoplasia) lesions. None of these changes are seen in wild type littermates. This animal model favors an antiproliferative role of ERβ. This role is further supported by our recent unpublished data showing that ERβ is never expressed in proliferating epithelial cells of prostate during normal development. These observations suggest that ligands specific for ERβ may be useful in the prevention and/or clinical management of prostatic hyperplasia and neoplasia." Weihua et al., supra at page 1, left column, 3rd paragraph.

The *Harris, et al.*, Endocrinology, 144(10, 4241-4249 (October 2003) reference relied upon by the Examiner is dated after the earliest priority date claimed for the present application of April 21, 2003. The *Harris, et al.* reference is directed toward the role of ER-beta, if any, in mediating the bone-sparing activity of estrogen on the rat skeleton and ER-beta's effect, if any, on ovulation or ovariectomy induced weight gain. Further, *Harris, et al.* concludes the ER beta selective agonist ERB-041 has a dramatic beneficial effect in the HLA-B27 transgenic rat model of inflammatory bowel disease and the Lewis rat adjuvant-induced arthritis model.

The pending claims in the present application are directed toward selectively agonizing ER-beta for purposes of treating benign prostatic hyperplasia. The prostate is different tissue and BPH is a different disease than discussed in *Harris, et al.*

The development of ER-α (*Korach*, Science, 266, 1524-1527 (1994)) and ER-β (*Krege, et al.*, Proc. Natl. Acad. Sci. USA, 95, 15677-15682 (1998)) knockout mice demonstrate that ER-β has different functions in different tissues. ER-β knockout mice develop prostatic hyperplasia with aging, which strongly evidences that ER-β normally protects against abnormal growth (*Krege, et al.*, (1998)). ERβ was expressed in the prostate of the ER-alpha knockout mice suggesting a distinct role for ERβ in the prostate in male mice (*Couse, et* al., Endocrinology, 138, 4613-4621 (1997)). Estrogen receptor-beta (ERβ), is preferentially expressed in the prostate and maintains characteristics that are different from ERα.

The report published by *Weihua, et al.*, PNAS, 98, 6330-6335 (2001) showed greater mitotic stain in the ventral prostate of ERβ knockout mice. Furthermore, this report shows compelling data for the metabolite of dihydrotestosterone, called 5α-androstane, 3β, 17β-a-diol, as one of the endogenous ligands that bind ERβ. This report evidences the validation of ER-beta modulation (agonism) for applications in prostate disease or pathologies (such as BPH), where the presence of ERβ receptors in the appropriate tissue compartment, lends itself for modulation using small molecule ligands that bind to ERβ and induce its transcriptional function.

(7) The quantity of experimentation needed. The Examiner's position is: The amount of experimentation is expected to be high and unpredictable.

Applicants' position:

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplates, 35

U.S.C. 112 is satisfied.

For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement. The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are merely factors in this consideration and are not the controlling factors. Time and difficulty of experiments are not determinative if they are merely routine.

Correlation refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.

A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> "Based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

Applicants respectfully contend the "quantity" of experimentation is not the test. Additional experimentation, by those skilled in the art, is routine. See, for example, reference BG (WO 97/09548), US 5,958,710 and particularly column 10, line 47 through column 12, line 32 where ligand binding affinity in binding saturation experiments and in binding competition experiments are described; and Reference CF, *Meyers, et al.*, J. Med. Chem., 44(24), 4230-4251 (2001), at page 4236 discloses biological results of receptor binding studies and structure-binding

affinity relationships. The *Harris, et al.*, Endocrinology, 144(10) 4241-4249 (2003) reference cited by the Examiner evidences the routine nature of *in vitro* and *in vivo* small animal model assays. The specification, in addition, provides a reasonable amount of guidance with respect to the direction in which experiments should proceed. The competition ER binding assay protocol and results (specification at page 103-104) and the methods of use and dosages (specification at page 107-108) affords more than a reasonable amount of guidance in which further experiments should proceed.

Further, as referenced above (U.S. Patent 7,217,734; U.S. Application Serial No. 10/493,092 IFW Declarations by Blake Neubauer and Venkatesh Krishnan 10/27/06) establishes a correlation between *in vitro* data and *in vivo* small animal BPH treatment activity for similarly structured compounds to those claimed in the present application.

Applicants respectfully contend, based on all of the factors and matters disclosed above, Claim 42 in view of the specification fully complies with the enablement requirement of 35 U.S.C. 112, first paragraph.

Rejection Under 35 U.S.C. 103

Claims 1, 3, 4, 5, 17, 38, 42, 43 and 45 stand rejected under 35 U.S.C. 103(a) over WO/2003/044006, U.S. equivalent 7,217,734 B2. The cited reference is stated to be prior art under 35 U.S.C. 102(e), and separately homologs for those instances where G is CH_2 in the '734 patent and G is $CHCH_3$ in the claims of the present application.

Applicants respectfully traverse these rejections and request reconsideration in view of the copies of the Assignment documents for the present application from the provisional and the International application which are enclosed as Exhibits with this amendment. It should be seen that both the provisional and the International application are assigned to Eli Lilly and Company and the enclosed Assignment exhibits demonstrate that at the time the present invention was made, the inventors were under an obligation to assign their invention to Eli Lilly and Company. Applicants respectfully contend the enclosed Assignment exhibits evidence the cited reference is not available as 35 U.S.C. 102(e)/103(a) prior art against the presently claimed invention under 35 U.S.C. 103(c).

Applicants were all employees of Eli Lilly and Company at the time the present invention was made. They were under an obligation to assign any inventions made to Eli Lilly and Company. Attached as Exhibit 1 is a copy of the Assignment of the inventions disclosed in U.S. provisional patent application by the inventors to Eli Lilly and Company. Assignment Exhibit 1

is recorded at Reel 017859, Frame 0255 (6 pages). Attached as Exhibit 2 is a copy of the Assignment of the inventions of the present patent application showing title is held by Eli Lilly and Company. Assignment Exhibit 2 is recorded at Reel 020022, Frame 0687 (5 pages). Also attached as Exhibits 3, 4 and 5 are copies of the Assignments of the inventions disclosed in provisional patent applications and the International patent application of the cited reference evidencing Eli Lilly and Company as the assignee of the inventions and patent. The Assignment for WO2003/044006 (Exhibit 5) is recorded at Reel 015946, Frame 0324 (8 pages). The Assignment, Exhibit 3 (first provisional patent application) is recorded at Reel 012625, Frame 0498 (3 pages). The Assignment, Exhibit 4 (second provisional patent application) is recorded at Reel 012867, Frame 0779 (6 pages). Because the inventors of the present invention were, at the time the invention was made, under an obligation to assign and did assign such invention to Eli Lilly and Company, Applicants respectfully contend they have clearly demonstrated under 35 U.S.C. 103(c), the reference is not available as a 102(e)/103(a) reference against the present application.

Applicants further contend the disqualification of *Dodge, et al.* (WO/2003/0044006, U.S. equivalent 7,217,734 B2) as a prior art reference under 35 U.S.C. 103(c) in a rejection under 35 U.S.C. 103(a) renders the homolog rejection, page 14-17 of the August 16, 2007 Office Action no longer applicable.

Double Patenting Issues

All pending claims stand rejected under the non-statutory judicially created obviousness-type double patenting doctrine over Claims 1-15, 17-22, 24-28, 31, 35, 37-39 and 45-51 of U.S. Patent 7,217,734 B2. Applicants respectfully traverse this rejection and request reconsideration.

Initially, Applicants point out the *Dodge, et al.*, U.S. Patent 7,217,734 B2 has been eliminated for obviousness purposes of 35 U.S.C. 102(c)/103(a) under the provisions of 35 U.S.C. 103(c). Applicants respectfully contend the claims in the noted U.S. Patent are directed toward compounds, formulations and certain methods of use where G is $-CH_2-$, $-CH_2-CH_2-$, or $-CH_2-CH_2-CH_2-$. Based on the restriction and provisional election in the present application, the $-CH_2-$ option from *Dodge, et al.* is at issue. The presently claimed invention is directed toward cyclopentane fused benzopyrane compounds where G is, among other defined options a $-CH(CH_3)-$. The G substituent in *Dodge, et al.* and the G substituent in the presently claimed invention are similarly positioned at the apex of the cyclopentane fused ring portion of the molecule.

Applicants respectfully contend the compounds are structurally distinct, as claimed, and no *prima facie* case of obviousness is present. Necessarily, Applicants contend the claims of *Dodge, et al.* do not support a *prima facie* case of obviousness-type double patenting against the presently claimed compounds.

Dodge, et al. does not teach, suggest or provide motivation to modify the apex carbon atom in the cyclopentane fused ring portion of the compounds.

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."

Compounds which are homologs are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. Homologs which are far removed from adjacent homologs may not be expected to have similar properties. Homology should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed "as a whole." In *In re Grabiak*, 769 F.2d 729, 226 USPQ 871 (Fed. Cir. 1985) (substitution of a thioester group for an ester group in an herbicidal safener compound was not suggested by the prior art).

Any teaching or suggestion in the reference of a preferred species or subgenus that is different in structure may weigh against the claimed modification and thus against a determination of obviousness. *In re Baird*, 16 F.3d at 382-83, 29 USPQ2d at 1552; *In re Jones*, 958 F.2d at 350, 21 USPQ2d at 1943 (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic). For example, teachings of preferred species of a complex nature within the disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus.

Applicants respectfully contend the -$CH(CH_3)$- definition for G in the presently claimed invention is not a homolog of -CH_2- in the context of the present application. Applicants contend modifying a cyclopentyl fused ring portion of a molecule by the addition of an exomethyl substituent group, and particularly at the apex carbon atom, does not create a homologous series as is commonly understood by one skilled in the art. Rather, one skilled in the art views such a modification as the addition of a substituent at a previously unsubstituted position on the molecule. The present situation is not a matter of extending a methyl linker to an ethyl linker or

extending a methyl substituent to an ethyl substituent. To have a homologous series, the presence of at least one member of such a group (i.e. an n of 1) is a fundamental requirement. Adding a methyl substituent at a position (10 position consistent with *Dodge, et al.* lexicon) of a cyclopentyl fused ring portion of a benzopyrans compound where no substituent was previously contemplated does not make such substituent a homolog. Applicants contend this is an improper, and scientifically incorrect, application of the organic chemistry homologous series concept.

Dodge, et al. discloses optional substituents (Y^2 and Y^3) on the cyclopentyl, cyclohexyl or cycloheptyl fused ring portion of the molecule at the 11, 12 or 13 positions (see column 5, line 35 through column 6, line 14 of *Dodge, et al.*). At column 7, line 55 to bottom of column 7, *Dodge, et al.*, teaches away from Y^2 and Y^3 substituents stating a preference for Y^2 and Y^3 are both H (Preferred embodiment (3)). Applicants contend this teaching away by *Dodge, et al.*, would lead one skilled in the art away from modifying alternative positions of the cyclopentyl fused ring portion of the molecules as has been accomplished with the presently claimed compounds, particularly by the addition of a substituent.

Necessarily, Applicants respectfully contend a *prima facie* case of obviousness does not exist for the presently claimed invention.

Conclusion

Applicants believe they have addressed each of the objections and rejections set forth by the Examiner in the Office Action, dated August 16, 2007. To the extent Applicants have inadvertently overlooked one or more of the objections or rejections set forth by the Examiner, Applicants respectfully request an opportunity to file a Supplemental Amendment in order to address such maters or to further respond in a subsequent communication.

In view of the remarks made herein, Applicants respectfully request favorable reconsideration of this application.

Respectfully submitted,

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